Letter to the Editor

Development of a prediction model for a severe reaction in cow’s milk challenges

Dear Editor,

In addition to their treatment purposes, which is for the definitive diagnosis of a food allergy or for the discernment of tolerance to the allergen, oral food challenges (OFCs) are performed to determine the threshold dose of food allergens for risk-assessment or minimal avoidance. More severe reactions tend to be provoked in these OFC settings. We have already reported a model for predicting severe allergic reactions provoked in boiled egg challenges. In the present study, we developed a model for predicting a severe reaction to a milk OFC. This new model was developed via a similar method to that used for the egg challenge.

An open OFC of milk was performed in accordance with the Japanese Guideline for Food Allergy throughout the study period. Raw cow’s milk was administered in a gradient dose (typically 4 to 5 doses from 0.2-0.5-1-2-5-10-20 ml) every 30–40 min. The challenge was stopped if the patient exhibited an objective allergic reaction corresponding to >5 points of the total score (TS) of Anaphylaxis Scoring Aichi (ASCA). To quantify the overall severity of the result of OFCs, the TS/Pro was applied, which was calculated by dividing the TS by the cumulative protein dose (Pro) of milk (3.3% of whole milk) administered before the appearance of symptoms. We divided patients in the development dataset into two groups (severe cases and non-severe cases) based on the median value of the TS/Pro of the development dataset.

The development dataset was obtained from OFCs to cow’s milk from April 2012 to May 2013. During this period, 220 OFCs to milk were conducted, and 144 (65.5%) of those were positive. The appropriate laboratory data (specific IgE to milk and total IgE) collected within 180 days from OFC were missing in 37 cases, and 10 OFCs performed during the OIT were also excluded. As a result, 97 cases were analyzed. To validate this model in an independent clinical setting (validation dataset), 95 consecutive OFCs to milk (70 positive and 25 negative) with appropriate data and conditions from June 2013 to March 2014 were analyzed in a prospective manner.

This study was approved by the institutional review board of Aichi Children’s Health and Medical Center. All analyses were performed with the STATA software program (version 12.1 for Mac; STATA Inc., College Station, TX, USA). For all analyses, a 2-sided probability value below 0.05 was considered to indicate statistical significance.

The characteristics of the datasets are shown in Supplementary Table 1. Based on the median value of TS/Pro in the development dataset, we defined severe cases as TS/Pro ≥80 (n = 48) and non-severe cases as <80 (n = 48). The result of a stepwise forward logistic regression analysis including all factors in Supplementary Table 1 revealed three factors—milk specific IgE (sIgE, class), complete avoidance and total IgE (tIgE) < 1000 IU/mL—to be independently associated with severe cases. We then constructed a prediction score of logistic regression model, in which the logistic coefficient (β) of each of the three factors was directly used, and a simple scoring model by approximating the logistic coefficient (β). The simple scoring model consisted of the base points for milk-sIgE (1 point per class) and 2 points each for tIgE < 1000 IU/mL and complete avoidance, resulting in a maximum of 10 points (Table 1).

The prediction score was found to be significantly correlated with the TS/Pro (Fig. 1). To discriminate severe cases, the area under the ROC (Receiver operating characteristic) curve (AUC) was 0.81 (95% confidence interval [CI], 0.72 to 0.89) for the simple scoring model, which was almost identical to the value of 0.81 obtained from the logistic regression model (95% CI, 0.73 to 0.90) in the development dataset. Furthermore, the discriminatory ability of the simple scoring model was superior to the milk sIgE titer (class) only (AUC = 0.68, 95%CI, 0.57 to 0.77, p < 0.001, Supplementary Fig. 1).

In the validation dataset, the area under the ROC curve was 0.88 (0.81–0.95) for the simple scoring model, which tended to be superior in its discriminatory ability in comparison to the milk-sIgE class alone (AUC = 0.81, 0.72 to 0.91) but not to a statistically significant degree (p = 0.24, Supplementary Fig. 1), and the Hosmer–Lemeshow statistic was not significant in either dataset. Among the 12 OFCs with a prediction score of ≥8 in the validation dataset, 9 OFCs (75.0%) resulted in severe cases (TS/Pro ≥80). In contrast, 43/44 OFCs (97.7%) with a prediction score of ≤5 presented resulted in a non-severe outcome or negative results. The sensitivity and specificity of each cutoff are shown in Supplementary Table 2.

The specific IgE titer, tIgE and complete avoidance of antigen have been identified as independent risk factors of severe cases

Table 1

<table>
<thead>
<tr>
<th>Class</th>
<th>OR (adjusted)</th>
<th>SE</th>
<th>Score point</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.24</td>
<td>2.25</td>
<td>0.63</td>
<td>9.47</td>
</tr>
<tr>
<td>0.25–0.79</td>
<td>2.52</td>
<td>0.81</td>
<td>12.4</td>
</tr>
<tr>
<td>≥0.80</td>
<td>2.52</td>
<td>0.81</td>
<td>12.4</td>
</tr>
</tbody>
</table>

Log(p/1–p) = −6.4 + 0.78 × Class + 2.52 × (tIgE < 1000) + 2.25 × (complete avoidance).

Simple scoring model: 1 × Class + 2 × (tIgE < 1000) + 2 × (complete avoidance).

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in challenges with other food allergens, such as heated egg \(^2\) (Although we evaluated “milk-sIgE/total IgE” as an alternative factor, it did not improve discriminatory ability of the model). However, in the present study, a better discriminatory ability for predicting severe results in milk challenges than with sIgE (class) alone was observed only in the development dataset, not in the validation dataset.\(^2\) Validation dataset included OFC-negative patients (25/95). Their median milk sIgE titer was 2.2 kUA/L, which was significantly lower than that of OFC-positive patients (14.8 kUA/L). This increased the discrimination ability of sIgE alone in the validation dataset (AUC \(= 0.81\)). Although not statistically significant, the AUC of simple scoring model in the validation dataset was superior (AUC \(= 0.88\)) to that. As a result, we concluded that this was the best available prediction model based on the sIgE and clinical information.

We usually instruct patients with low TS/Pro to start ingesting a small amount of the allergen.\(^5\) This dietary instruction is applied to patients expected to be able to ingest \(>2\) mL of milk safely.\(^6\) For example, when a total of \(8.5\) mL milk (Pro = 0.28) provoked localized urticaria (TS = 5, TS/Pro = 18), we allowed the patient to start with 2 mL of milk. Most (about 90%) patients with a prediction score of \(\leq 5\) are expected to be such non-severe cases. However when the same dose of milk induced localized urticaria plus apparent wheezing (TS = 25, TS/Pro = 89), we instructed the patient to continue complete avoidance. Most (about 80%) patients with a prediction score of \(\geq 8\) are expected to be such severe cases.

In conclusion, our prediction model showed good discrimination of severe cases based on the TS/Pro. It may therefore be clinically effective for many pediatric allergists to encourage a desirable OFC and to avoid high risk OFCs.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.alit.2016.11.005.

Conflict of interest

The authors have no conflict of interest to declare.

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References